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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/534,171	05/06/2005	Paola Branduardi	3912.1000-000	5195
21005	7590	07/24/2008	EXAMINER	
HAMILTON, BROOK, SMITH & REYNOLDS, P.C. 530 VIRGINIA ROAD P.O. BOX 9133 CONCORD, MA 01742-9133			VOGEL, NANCY TREPTOW	
			ART UNIT	PAPER NUMBER
			1636	
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			07/24/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)
	10/534,171	BRANDUARDI ET AL.
	Examiner	Art Unit
	NANCY VOGEL	1636

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) Responsive to communication(s) filed on 18 April 2008.
 2a) This action is FINAL. 2b) This action is non-final.
 3) Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) Claim(s) 22,24-30,32,34,36 and 38-41 is/are pending in the application.
 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
 5) Claim(s) _____ is/are allowed.
 6) Claim(s) 22,24-30,32,34,35 and 38-41 is/are rejected.
 7) Claim(s) _____ is/are objected to.
 8) Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) The specification is objected to by the Examiner.
 10) The drawing(s) filed on _____ is/are: a) accepted or b) objected to by the Examiner.
 Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
 Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
 11) The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
 a) All b) Some * c) None of:
 1. Certified copies of the priority documents have been received.
 2. Certified copies of the priority documents have been received in Application No. _____.
 3. Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|---|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. _____ . |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08)
Paper No(s)/Mail Date <u>12/27/07</u> . | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

Claims 22, 24-30, 32, 34, 36, 38-41 are pending in the case.

Receipt of the Information Disclosure Statement on 12/27/07 is acknowledged.

Election/Restrictions

Applicant's election of the species of SEQ ID NO:1 and SEQ ID NO:69 in the reply filed on 9/19/07 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

Claims 22, 24-26, 28-31, 32, 34, 36, 39-41 are rejected under 35 U.S.C. 103(a) as being unpatentable over Brambilla et al. (WO 00/41477) (cited by applicants) in view of (Brake et al. (Proc. Natl. Acad. Sci. USA, 81, 4642-4646, 1984) or Stark et al. (EMBO J., 5, 1995-2002, 1986)..

This rejection is maintained essentially for the reasons made of record in the previous Office action, mailed 12/13/07, with slight modifications necessitated by applicant's amendments to the claims:

Brambilla et al. disclose method for production of a protein comprising the steps of culturing a *Zygosaccharomyces bailii* (*Z. bailii*) strain, expressing a protein such as a recombinant protein, and isolating the protein (see page 11, line 22-28). The reference discloses that appropriate sequence may be used for secretion (see page 3, lines 15-24). The reference discloses using an extra-chromosomal plasmid, derived form an endogenous episomal plasmid from *Z. bailii* strain, including sequences for replication, stabilization or plasmid copy number control (see claims, see Example 1-2). The reference discloses that the TPI (triphosphate isomerase) or the GAP (glyceraldehyde phosphate dehydrogenase) promoter of *S. cerevisiae* may be used (page 12 line 17-20). The reference discloses that strains such as ATCC 36947 or ATCC 60483 may be used (page 11 lines 20,21). The reference discloses that the DNA sequence coding for protein may be derived from any prokaryote or eukaryote (page 11 lines 22- page 12 line 16). The reference discloses that the strain may be cultivated in chemically defined medium (page 15).

The difference between the reference and the instant claims is that the protein is secreted and a signal sequence such as the signal sequence shown in SEQ ID NO:1, or the pre-pro alpha-factor of *S. cerevisiae*, or the pre-sequence of the alpha-subunit of the K1 killer toxin of *D. lactis*, is operably linked to the DNA encoding the protein.

However, Brake et al. disclose the signal or prepro-sequence of the alpha factor mating pheromone encoding gene and its use to direct secretion of heterologous genes in yeast. Stark et al. disclose the signal sequence of the alpha-subunit of the K1 killer toxin of *K. lactis*, and its function in directing the secretion of a protein product operably linked.

It would have been obvious to one of ordinary skill in the art to have placed the signal sequence of Stark et al. . in operable linkage to a protein of interest and a promoter of interest, since Brambilla et al. disclosed that appropriate sequences for the localization of a protein of interest may be used, and since Stark et al. disclose such a sequence for secretion of a protein of interest. One would have been motivated to do so by the desire to obtain secreted, and therefore more easily purified, heterologous proteins. Based upon the teachings of the cited references, the high skill of one of ordinary skill in the art, and absent evidence to the contrary, there would have been a reasonable expectation of success to result in the claimed invention.

It would have been obvious to have utilized a well known signal sequence such as that obtained from the alpha-factor encoding gene of the *S. cerevisiae* as disclosed by Brake et al., since the Brambilla et al. reference clearly suggests the use of standard expression sequences for direction of the secretion of proteins of interest, and since Brake et al. discloses such as sequence for use in yeast. One would have been motivated to do so by the desire to secrete a protein from the *Z. bailii* yeast disclosed as useful by Brambilla et al., since secreted proteins are free of contamination by host proteins, and since their purification is normally easier than proteins contained within a

cell. Based upon the teachings of the cited references, the high skill of one of ordinary skill in the art, and absent evidence to the contrary, there would have been a reasonable expectation of success to result in the claimed invention.

Applicant's arguments filed 4/18/08 have been considered but have not been found convincing.

Applicants have argued that the use of the claimed protein expression process yields unexpected results, as evidence by side-by-side comparisons shown in Figures 5 and 6. However, the results that are disclosed are not commensurate in scope with the instant claimed method, since they only show one particular plasmid construct. Furthermore, there is no evidence that the cell number is the same for *Z. bailii* strain and the *S. cerevisiae* strain in the results shown in Fig. 6, and therefore it is not clear whether the results shown therein indicate that more protein is secreted per cell for the *Z. bailii* than *S. cerevisiae*. Therefore the rejection is maintained.

Claim 27 is rejected under 35 U.S.C. 103(a) as being unpatentable over Brambilla et al. (WO 00/41477) (cited by applicants) in view of (Brake et al., Proc. Natl. Acad. Sci. USA, 81, 4642-4646, 1984) or Stark et al. as applied to claims 22, 24-26, 28-31, 32, 34, 36, 39-41 above, and further in view of Jacobson et al. (WO9204461).

Brambilla et al. and Brake et al. and Stark et al. are cited essentially for the reasons set forth above.

The difference between the references and the instant claim is that a particular DNA sequence, ie. at least 35 nucleotides of the sequence that is shown in SEQ ID NO:69, is present in the plasmid.

However, Jacobson et al. disclose a DNA sequence which comprises at least 35 nucleotides of the sequence shown in SEQ ID NO:69 (see alignment attached). Jacobson et al. disclose that the DNA encodes a particular antigen. It would have been obvious to one of ordinary skill in the art to have placed the DNA disclosed by Jacobson et al. in the plasmid and strain disclosed by Brambilla et al. and Brake et al. or Stark et al., since Brambilla disclose that any DNA encoding a protein of interest may be expressed in the disclosed yeast strains, and since Jacobson disclose such a DNA encoding a protein of interest. One would have been motivated to do so by the disclosure of Brambilla et al. which discloses that the *Z. bailii* yeast has certain advantages for the expression of proteins of interest, and since Jacobson et al. disclose such a protein which is useful for production of antigens of a organism of economic importance. Based upon the teachings of the cited references, the high skill of one of ordinary skill in the art, and absent evidence to the contrary, there would have been a reasonable expectation of success to result in the claimed invention.

Applicants have argued that the claim 27 depends on base claim 22 as amended and is non-obvious for the same reasons as base claim 22. Therefore for the same reasons as set forth above, applicant's arguments are not found convincing and the rejection is maintained.

The following are new rejections not necessitated by applicant's amendments:

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 22, 24-30, 32, 34, 36, 38-41 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

To provide evidence of possession of a claimed genus, the specification must provide sufficient distinguishing identifying characteristics of the genus. The factors to be considered include disclosure of compete or partial structure, physical and/or chemical properties, functional characteristics, structure/function correlation, methods of making the claimed product, or any combination thereof. In this case, claims 22, 24-30, 32, 34, 35, 38-41 are directed to a process for production of a protein using *Z. bailii* strain transformed with a vector. Claim 25 recites that the plasmid vector is derived from an endogenous plasmid from a *Z. bailii* strain. Claim 27 recites that the plasmid comprises at least 35 nucleotides of any of the sequences shown in SEQ ID NO:63-71, which are apparently fragments of an endogenous plasmid from *Z. bailii*. While the specification has adequate written description of the plasmid actually isolated from *Z. bailii*, there is no disclosure on the structural limitations of the genus represented by the

any plasmid vector that can function in the claimed process, or any plasmid isolated from *Z. bailii* strains, or any plasmid that can function in the claimed process and which comprises at least 35 nucleotides of the SEQ ID NO:63-71. There is no identification of sequences necessary for plasmid replication and maintenance in *Z. bailii*. Further, there is no disclosure of the activity of the above-mentioned derivatives. One skilled in the art would conclude that the disclosure of a single endogenous episomal plasmid from a *Z. bailii* strain is not representative of the undefined genus of derivatives recited in the claims. Accordingly, in the absence of sufficient recitation of distinguishing identifying characteristics, the specification does not provide adequate written description of the claimed genus. Therefore, the inventor, at the time the application was filed was not in possession of the broad genus comprising derivatives of the endogenous plasmid bacterial RNAP, derivatives of a bacterial RNAP homologous RNA-exit-channel, or derivatives of eukaryotic RNAP, or fragments thereof, needed to practice the claimed invention.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 25 and 27 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 25 and by dependence claim 27 are vague and indefinite in the recitation of "derived from". "Derived" is a term that is non-specific and relative in nature for which Applicant provides no definition. It provides no clarity as to what Applicant's claimed invention includes and what it does not include. Without a more specific definition, it is impossible to determine what and how many derivations comprise the invention. The nature and number of the derivations to arrive at the invention Applicant seeks to protect with the patent are not established such that a person skilled in the art would be apprised of the metes and bounds of the claims. The limits of the inventions cannot be discerned and others could not know if they were infringing Applicant's claim.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to NANCY VOGEL whose telephone number is (571)272-0780. The examiner can normally be reached on 7:00 - 3:30, Monday - Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph Woitach can be reached on (571) 272-0739. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/NANCY VOGEL/
Primary Examiner, Art Unit 1636

NV
7/15/08